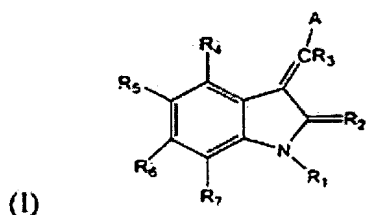


Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF, or PDGF on cells *in vivo* or *in vitro*, modulating tyrosine kinase signal transduction or treating or preventing an abnormal condition, said method comprising administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more indolinone compounds of Formula I:



wherein,

R₁ is H or alkyl;

R₂ is O or S

R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen alkyl-, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

A is selected from the group consisting of a ~~4,5,6,7-tetrahydroindole~~ 4,5,6,7-tetrahydroindole and a five-membered heteroaryl ring, wherein said ~~five-membered~~ five-membered ring is selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, ~~1,3,4-thiadiazole~~ 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, ~~1,2,3,5-thiadiazole~~

1,2,3,5-thiadiazole, and tetrazole, wherein said five-membered ring and said tetrahydroindole are optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R.

2. (Currently Amended) The method of claim 1, wherein said A is selected from the group consisting of thiophene, ~~pyrrole~~ pyrrole, and 4,5,6,7-tetrahydroindole, optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR.

3. (Original) The method of claim 1, wherein said indolinone compounds of Formula I are selected from the group consisting of Compound II, Compound III, Compound IV, Compound V, Compound VI, Compound VII, and Compound VIII.

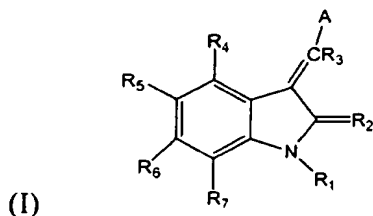
4. (Original) The method of claim 1, wherein said composition further comprises one or more pharmaceutically acceptable excipients in a formulation.

5. (Original) The method of claim 4, wherein said formulation is at least one of parenteral, oral, or topical formulation.

6. (Original) The method of claim 1, wherein said effective amount comprises an amount in the range of from about 1 to about 1000 mg/m²/day.

7. (Original) The method of claim 1, wherein said abnormal condition is endometriosis and/or arthritis.

8. (Currently Amended) A method of identifying one or more indolinone compounds of Formula I



that inhibit growth factor-stimulated cell proliferation comprising the following steps:

- (a) contacting cells with one or more indolinone compounds;
 - (b) contacting said cells with one or more growth factors selected from the group consisting of VEGF, PDGF, and FGF;
 - (c) monitoring an inhibitory effect on growth factor stimulated cell proliferation;
- and
- (d) identifying indolinone compounds of formula I that inhibit growth factor-stimulated cell proliferation,

wherein,

R₁ is H or alkyl;

R₂ is O or S;

R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

A is selected from the group consisting of 4,5,6,7-tetrahydroindole, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-

oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

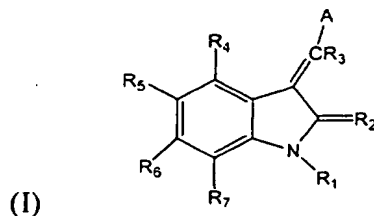
R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R.

9. (Original) The method of claim 8, wherein said cells are endothelial cells and are contacted with VEGF in step (b).

10. (Original) The method of claim 8, wherein said cells are smooth muscle cells and are contacted with PDGF in step (b).

11. (Original) The method of claim 8, wherein said cells are endothelial cells and are contacted with FGF in step (b).

12. (Currently Amended) A method of identifying one or more indolinone compounds of Formula I



that are active in an adjuvant arthritis model in rats comprising the following steps:

(a) administering said one or more indolinone compounds to said rats;

(b) monitoring in said rats one or more effects selected from the group consisting of ear nodulation, tail nodulation, nose swelling, paw swelling and ballanitis; and

(c) identifying indolinone compounds of formula I that are active in an adjuvant arthritis model in rats,

wherein,

R₁ is H or alkyl;

R₂ is O or S;

R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

A is selected from the group consisting of 4,5,6,7-tetrahydroindole, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

n is 0-3;

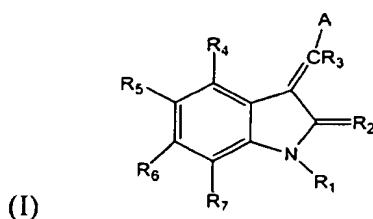
R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R.

13. (Original) The method of claim 12, wherein said one or more compounds are administered at a concentration in the range of from about 1 to about 1000 mg/m²/day.

14. (Currently Amended) A method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells comprising administering to a patient in need of such treatment a composition comprising a therapeutically effective amount of one or more compounds of formula I which inhibit VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells,

wherein said composition optionally includes one more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:



wherein,

R₁ is H or alkyl;

R₂ is O or S;

R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

A is selected from the group consisting of 4,5,6,7-tetrahydroindole, thiophene, pyrrole, pyrazole, ~~imidazole~~, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said group is optionally substituted with one or more substituents

selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

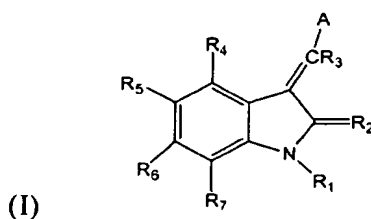
n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R.

15. (Currently Amended) A method of treating arthritis comprising or preventing an abnormal condition by administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more compounds of formula I which treat arthritis,

~~wherein said abnormal condition is selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, wherein said composition optionally includes one or more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:~~



wherein,

R₁ is H or alkyl;

R₂ is O or S;

R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

A is selected from the group consisting of 4,5,6,7-tetrahydroindole, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, ~~1,3,4-oxadiazole~~, ~~1,2,3,4-oxatriazole~~, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, ~~1,2,5-thiadiazole~~, ~~1,3,4-thiadiazole~~, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, CONRR', and (CH₂)_nONRR';

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

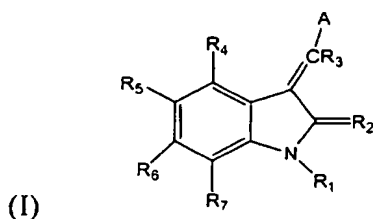
R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R.

16. (Canceled)

17. (Currently Amended) A method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells *in vitro*, comprising:

a) contacting said cells with one more compounds of formula I which inhibit VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells *in vitro*,

wherein said composition optionally includes one more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation:



wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, $CONRR'$, and $(CH_2)_nONRR'$;

A is selected from the group consisting of 4,5,6,7-tetrahydroindole, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said group is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, $CONRR'$, and $(CH_2)_nONRR'$;

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO₂, and (CH₂)_nCO₂R;

- b) measuring the activity of VEGF, FGF, or PDGF; and
- c) comparing said activity of VEGF, FGF, or PDGF to cells that have not been contacted with one more compounds of formula I.